JACC Vol. 23, No. 1
January 1994:209–18

Comparative Efficacy of Three Indexes of Left Ventricular Performance Derived From Pressure-Volume Loops in Heart Failure Induced by Tachypacing

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Objectives. The purpose of this study was to serially evaluate the response and variability of the end-systolic pressure-volume relation, the left ventricular end-diastolic volume–peak positive first derivative of left ventricular pressure (dP/dt) relation and the left ventricular end-diastolic volume–stroke work relation in the development of progressive left ventricular dysfunction.

Background. Evaluation of systolic performance of the failing left ventricle may be enhanced by using relatively load-insensitive measures of left ventricular performance. The end-systolic pressure-volume, left ventricular end-diastolic volume–peak positive dP/dt and left ventricular end-diastolic volume–stroke work relations adequately define left ventricular performance under multiple loading conditions, but efficacy has not been fully assessed in the failing heart, particularly in the intact circulation.

Methods. Fourteen dogs underwent instrumentation and rapid pacing to heart failure. Variably loaded pressure-volume beats were produced by inferior vena cava occlusion. The dogs were evaluated at baseline and at three progressively more severe levels of left ventricular dysfunction.

Results. There was a progressive increase in left ventricular volumes at end-diastole ([mean value ± SE] 60 ± 28 to 73 ± 29 ml, $p < 0.001$) and end-systole (39 ± 19 to 61 ± 27 ml, $p < 0.001$) during the 3 weeks of rapid pacing and a progressive decline in peak positive dP/dt (1,631 ± 410 to 993 ± 222 mm Hg/s, $p < 0.001$) and ejection fraction (37 ± 8% to 16 ± 11%, $p < 0.001$). There was a corresponding decline in the slope of each of the three relations: for end-systolic pressure-volume, 6.3 ± 2.2 to 2.8 ± 0.7 ($p < 0.05$); for left ventricular end-diastolic volume–stroke work, 61.9 ± 9.1 to 26.5 ± 2.4 ($p < 0.05$); and for left ventricular end-diastolic volume–peak positive dP/dt, 47.1 ± 13.6 to 20.31 ± 6.8 ($p < 0.05$). There was also a corresponding increase in position volumes: for end-systolic pressure-volume, 33.6 ± 3.9 to 61.2 ± 6.6 ml ($p < 0.05$); for left ventricular end-diastolic volume–stroke work, 46.2 ± 3.6 to 89.3 ± 7.6 ml ($p < 0.05$); and for left ventricular end-diastolic volume–peak positive dP/dt, 29.1 ± 19.1 to 68.6 ± 25.9 ml ($p < 0.05$). The relative degree of change in each of the three relations was similar as more severe heart failure developed. The coefficients of variation for position were significantly less than the variation for slopes. The response of volume intercepts was heterogeneous. For left ventricular end-diastolic volume–stroke work, the intercept increased as ventricular performance decreased. The intercept of the end-systolic pressure-volume relation was significantly more variable than the left ventricular end-diastolic volume–stroke work relation and did not change with progressive heart failure. The intercept for left ventricular end-diastolic volume–peak positive dP/dt was highly variable and showed no consistent changes as left ventricular function declined.

Conclusions. All three relations consistently describe changes in left ventricular performance brought about by tachypacing. Evolution of left ventricular dysfunction causes a decline in slope and a rightward shift of these relations. The position of the relation is the most sensitive and least variable indicator of left ventricular systolic performance.

(J Am Coll Cardiol 1994;23:209–18)

Evaluation of left ventricular contractility in patients with congestive heart failure is a persistent challenge. Changes in loading conditions, ventricular shape and valve function limit the efficacy of commonly used ejection phase indexes of function. To improve characterization of left ventricular contractility, relations between left ventricular end-systolic pressure and volume have been developed. First expressed as maximal elastance in isolated hearts, modifications of the end-systolic relation have been investigated in the intact circulation (1,2). Most commonly, the slope of the end-systolic pressure-volume relation has been utilized, but limitations have been noted (3–5). The slope and volume intercept are highly variable and difficult to compare among individual patients (5). The slope also may not be entirely independent of loading conditions and not linear at extremes of altered contractile state (6,7). To correct for this, evaluation of position of the relation at a fixed physiologic pressure has been proposed (8). Recently, two alternative forms of analysis of pressure-volume loops have been devel-

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Manuscript received August 31, 1992; revised manuscript received August 2, 1993, accepted August 27, 1993.

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0735-1097/94/$6.00

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oped: the relations between the peak positive first derivative of left ventricular pressure (dP/dt) and left ventricular end-diastolic volume and the relation between left ventricular stroke work and end-diastolic volume. Both have been reported to be linear and to respond to changes in contractility, but not loading conditions, within the normal physiologic range (9,10).

In a recent analysis, Little et al. (11) compared these three measures of left ventricular performance in normal hearts at baseline, at increased afterload and at one level of altered contractile state. They demonstrated that all three relations are adequate indicators of left ventricular performance. The left ventricular end-diastolic volume–stroke work relation was least variable but also least sensitive for detecting inotropic stimulation. It had a reproducible volume axis intercept that did not change with altered contractility. The left ventricular end-diastolic volume–peak positive dP/dt relation was most variable but also most sensitive for detection of inotropic stimulation. The end-systolic pressure-volume relation was intermediate in variability and responsiveness but also not entirely free of the effects of afterload as it changed position when afterload was increased (11).

If these measures of left ventricular performance are to be used to characterize heart failure, there is a need to investigate their efficacy and reliability in the failing heart (12,13). Several potential mechanisms could limit the efficacy of pressure-volume analysis in heart failure: 1) Elevated filling pressures may reduce the ability of caval occlusion to decrease end-systolic pressure and volume and lengthen the time necessary to achieve a load change; 2) longer time courses of load change could increase heart rate; 3) changes in arterial resistance with progressive failure could alter their response to caval occlusion; and 4) increasing chamber size may alter the response and affect calculation of derived values, such as the volume intercept. To assess these issues, the present study produced progressive levels of heart failure by tachypacing (14). The three measures of left ventricular performance (end-systolic pressure-volume, left ventricular end-diastolic volume–peak positive dP/dt and left ventricular end-diastolic volume–stroke work) were serially evaluated and compared at multiple levels of left ventricular dysfunction for agreement in detecting changes in left ventricular performance as well as variability.

Methods

Instrumentation. The protocol was approved by the Animal Care Committee of the University of Wisconsin, and all procedures for animal care conform to the "Position of the American Heart Association on Research Animal Use" adopted by the Association in November 1984. A total of 14 healthy female mongrel dogs with an average weight of 21.7 ± 1.7 kg (range 18.9 to 24.1) were utilized. The instrumentation was performed through a limited left thoracotomy, and after the heart was exposed, a P6.5 A Konigsberg pressure transducer and a 1.4-mm polyvinylchloride catheter were passed through the apex into the middle of the left ventricular cavity. Two similar catheters were placed in the middle of the left atrium through an incision in the atrial appendage. Two pairs of 5.0-MHz ultrasonic crystals were placed in a long- and short-axis orientation (15). Previous work by Rankin et al. (16) has shown that two crystal pairs oriented in this manner provide an accurate description of ventricular volume. A 16-mm hydraulic occluder cuff (R.E. Jones Co.) was fitted around the proximal inferior vena cava. External pacemaker leads (model 4951, Medtronic Inc.) were attached to the free wall of the left ventricle. The leads were connected to a modified Medtronic Spectrax Series pacemaker that was implanted in a pocket in the left upper thorax. All wires, leads and catheters were tunneled out to the neck and brought from the skin at this position. The dog was fitted with a special collar. The pericardium and thoracotomy were closed, and the dog was returned to the long-term care facility, where it recovered for 7 to 14 days.

Measurement sessions. Before each session the dog was lightly sedated with morphine and sodium thiopental. The trachea was intubated, and the dog was given low dose halothane (<0.5%). This dose of halothane has previously been shown to have minimal hemodynamic effects (17). On the dog's arrival at the laboratory, the pacemaker, if pacing, was turned off. All measurements were made after a minimum of 30 min of equilibration, with the dog in sinus rhythm. The dog was placed supine on its right side in the same position at each session. The fluid-filled catheters were attached to Statham P23ID pressure transducers that were balanced against air and a mercury manometer. The Konigsberg transducer signals were matched to the fluid-filled catheters.

The ultrasonic crystals were attached to a Crystal Biotech VF-1 system that was calibrated. The ultrasonic crystal signals, pressure tracings, electrocardiographic (ECG) monitor lead and peak positive dP/dt were displayed and recorded on a Gould 2800-S 8 channel physiologic strip chart recorder. The data were digitized using a Data Translation Device's DT-2821 analog to digital converter at 500 Hz and recorded into a 386 personal computer (Zenith Data Systems Corp.). Custom-developed acquisition software collected 10 consecutive beats of data during steady state conditions and averaged the data into one composite beat. The dog was then given atropine, 0.1 mg/kg, intravenously to eliminate vagal tone and thus eliminate any significant change in heart rate that might occur during the inferior vena cava occlusion. When steady state was achieved, data acquisition was repeated.

Pressure-volume loops. With use of the same computer system and previously validated custom-developed software, serial beats were acquired for 20 s after inflation of the hydraulic occluder cuff on the inferior vena cava. The caval occlusion caused a progressive decline in left ventricular end-systolic pressure, peak positive dP/dt and left ventricular volume. At the end of each 20-s run, caval occlusion was

released, and the dog was allowed to return to baseline hemodynamic status before the next run. Caval occlusions were repeated a minimum of three times for each condition (in 25% of the conditions, four or five runs were performed).

Heart failure protocol. At the conclusion of the baseline data acquisition session, the pacemaker was programmed to 175 beats/min, and the dog was returned to the long-term care facility. On day 2 the pacing rate was increased to 200 beats/min, and on day 3 it was increased to 215 beats/min, where it was maintained for the subsequent 5 days. At the end of 1 week, the dog was returned for a second measurement session similar to baseline. At the conclusion of measurements, the pacing rate was increased to 225 beats/min. After an additional week, the third measurement session was conducted. The pacing rate was increased to 240 beats/min, and 1 week later the final measurement session was performed. At the conclusion of the final session, the animals were killed with an overdose of potassium chloride. An autopsy was performed to determine placement of ultrasonic crystals and catheters.

Data analysis. Left ventricular volume was calculated from the ultrasonic crystal pairs using the formula for a modified ellipsoid (16):

$$V = \frac{\pi \times L \times S^2}{6},$$

where V = left ventricular volume; L = long-axis diameter; and S = short-axis diameter. Stroke volume was calculated from the ultrasonic crystal volumes as $V_{ED} - V_{ES}$, and ejection fraction (EF) was calculated as

$$EF\% = \frac{V_{ED} - V_{ES}}{V_{ED}} \times 100,$$

where V_{ED} = left ventricular volume at the R wave of the ECG monitor lead, and V_{ES} = left ventricular volume at its minimum. Cardiac output was estimated by multiplying heart rate by stroke volume. Arterial resistance was crudely estimated as (end-systolic pressure) −5 mm Hg divided by cardiac output. Stroke work was calculated by integration of each pressure-volume loop, as previously described by Glower et al. (10).

The slope (E_{ES}) of the end-systolic pressure-volume relation was calculated using the iterative technique of Kono et al. (18). To calculate the position volume of the end-systolic pressure-volume relation, the left ventricular volume associated with an end-systolic pressure of 75 mm Hg (V_{75}) was calculated as

$$V_{75} = V_{0-PV} + 75/E_{ES},$$

where V_{0-PV} = volume intercept.

The slope of the left ventricular end-diastolic volume–stroke work relation (M_{SW}) was calculated by a least-squares fit of the same beats used to calculate the end-systolic pressure-volume relation. The position volume of the left ventricular end-diastolic volume–stroke work relation was determined using a stroke work value of 1,000 mm Hg/×ml and calculated as

$$V_{1,000} = V_{0-SW} + 1,000/M_{SW},$$

where V_{0-SW} is the volume intercept of the left ventricular end-diastolic volume–stroke work relation.

The slope of the left ventricular end-diastolic volume–peak positive dP/dt relation, dE/dt max, was calculated by a least-squares fit similar to the left ventricular end-diastolic volume–stroke work relation (11). The position volume of the left ventricular end-diastolic volume–peak positive dP/dt relation was calculated using a peak positive dP/dt value of 1,000 mm Hg/s and the relation

$$V_{1,000} = V_{0-dP/dt} + 1,000/dE/dtmax,$$

where $V_{0-dP/dt}$ is the volume intercept of the left ventricular end-diastolic volume–peak positive dP/dt relation.

Statistics. For each condition, at least three runs were performed, and the mean values of the runs for slope, position and volume intercept were determined. From this, the coefficient of variation (SD/mean value) for each series of runs was calculated and expressed as a percent. Data were pooled from each dog at baseline and for each week of heart failure to allow calculation of pooled variation coefficients for each measurement type. The change in the coefficients of variation with progressive heart failure was evaluated with analysis of variance (ANOVA) of repeated measures. The coefficients of different measurement types were compared using the Student *t* test.

The values for slope, position and volume intercept were determined at baseline and for each week of developing heart failure. The significance of change of these values was calculated using ANOVA of repeated measures. Intergroup comparisons were made using the Newman-Keuls test. The percent change from baseline in the slope and position of each relation was determined for each week of progressively more severe left ventricular dysfunction. Similar percent change calculations were made for left ventricular ejection fraction and peak positive dP/dt. Correlations between ejection fraction and peak positive dP/dt were made with the slopes and positions using linear regression analysis. Correlations were also made between percent change of each of the slopes of the relations.

For hemodynamic and volumetric descriptions of ventricular performance that did not require variably loaded pressure-volume loops, the mean value for each level of heart failure was calculated and evaluated versus baseline using ANOVA of repeated measures and the Newman-Keuls test. All values are reported as mean value ± SE.

Results

The changes in left ventricular size and function caused by tachypacing are shown in Table 1. The values shown are in the rest state after equilibration but before any cardioactive drugs have been given. At baseline, after recovery from

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Table 1. Changes in Left Ventricular Size and Function Caused by Tachypacing

	Baseline	Week 1	Week 2	Week 3	p Value*
Heart rate (beats/min)	61 ± 19	59 ± 14	76 ± 27†	95 ± 20†	< 0.001
Systolic BP (mm Hg)	102 ± 25	101 ± 18	94 ± 16	87 ± 10†	0.03
LV end-diastolic pressure (mm Hg)	11 ± 4	15 ± 4	19 ± 6†	26 ± 6†	< 0.001
LV end-diastolic volume (ml)	60 ± 28	64 ± 28†	68 ± 29†	73 ± 29†	< 0.001
LV end-systolic volume (ml)	39 ± 19	48 ± 21†	56 ± 26†	61 ± 27†	< 0.001
Ejection fraction (%)	37 ± 8	26 ± 8†	21 ± 10†	16 ± 11†	< 0.001
+dP/dt (mm Hg/s)	1,631 ± 410	1,328 ± 310†	1,140 ± 286†	993 ± 222†	< 0.001
Estimated peripheral vascular resistance (dynes·s·cm^{-5})	3,089 ± 1,282	4,988 ± 2,311†	5,088 ± 2,853†	3,446 ± 2,773†	< 0.004
Long-axis/short-axis ratio	1.3 ± 0.1	1.3 ± 0.2	1.3 ± 0.2	1.3 ± 0.2	NS

*Analysis of variance of repeated measures. †$p < 0.05$ vs. baseline by the Newman-Keuls test. Values presented are mean value ± SE. BP = blood pressure; +dP/dt = peak positive first derivative of left ventricular pressure; LV = left ventricular.

the instrumentation operation, there was a mild reduction in left ventricular function. Tachypacing caused a significant and progressive increase in left ventricular end-diastolic and end-systolic volumes. However, there was no significant change in left ventricular geometry induced in this model. The long-axis/short-axis ratio remained constant. There was a significant decline in both ejection fraction and peak positive dP/dt. Systolic blood pressure slowly declined, becoming significantly lower only during week 3 compared with baseline. Left ventricular end-diastolic pressure increased progressively during the study, becoming significant during weeks 2 and 3. Heart rate also significantly increased at weeks 2 and 3. Estimated peripheral vascular resistance significantly increased during weeks 1 and 2 but declined to near baseline during the final week.

There was no change in the maximal heart rate produced by administration of atropine from baseline through the 3 weeks of heart failure: 119 ± 6, 120 ± 6, 118 ± 7 and 124 ± 7 beats/min, respectively (p = NS). Heart rate at the end of each run of variably loaded beats remained within ±10% of the beginning rate, and the amount of rate variation did not change as heart failure progressed. For each series of variably loaded beats, systolic pressure did not begin to decrease until left atrial pressure declined to a low value at each degree of severity of heart failure. For baseline and the three levels of heart failure systolic pressure began to decrease at a left atrial pressure of 4.3 ± 0.5, 6.1 ± 0.5*, 6.2 ± 0.6* and 6.1 ± 0.6* mm Hg (*$p < 0.05$ vs. baseline). As the severity of failure progressed, the number of beats required to lower left atrial pressure to the point where systolic pressure would decline increased. From baseline to the most severe level of failure, the number of beats was 5 ± 1, 6 ± 1, 18 ± 9 and 25 ± 10* (*$p < 0.05$ vs. baseline and week 1). The range of end-systolic pressures developed by vena caval occlusion progressively declined as heart failure became more severe: 41 ± 3, 32 ± 3, 31 ± 5 and 18 ± 1* mm Hg (*$p < 0.05$ vs. all other conditions).

The pooled coefficients of variation for the slopes of the three relations (all runs) were 8.4 ± 1.1* (end-systolic pressure-volume), 7.1 ± 0.9* (left ventricular end-diastolic volume–stroke work) and 11.8 ± 1.6 (left ventricular end-diastolic volume–peak positive dP/dt) (*$p < 0.05$ vs. the slope of the left ventricular end-diastolic volume–peak positive dP/dt relation). Thus, there was slightly, but significantly more variation in the slope of the left ventricular end-diastolic volume–peak positive dP/dt relation. There was no systematic increase in variation as heart failure became more severe.

The pooled coefficients of variation for the position of each of the three relations were similar: V_{75} (end-systolic pressure-volume) 3.4 ± 0.9, $V_{1,000}$ (left ventricular end-diastolic volume–stroke work) 3.8 ± 0.7 and $V_{1,000}$ (left ventricular end-diastolic volume–peak positive dP/dt) 5.0 ± 0.9. There was also no consistent change in the coefficient of variation for any of the relations from baseline to the most severe levels of heart failure. In comparing the slope of each relation to position, the coefficient of variation for position was significantly less than it was for the slope for all three relations ($p < 0.05$).

The pooled coefficients of variation for the volume intercept of each relation were 21.0 ± 3.7 (end-systolic pressure-volume), 4.0 ± 1.0 (left ventricular end-diastolic volume–stroke work) and 106 ± 36 (left ventricular end-diastolic volume–peak positive dP/dt). The volume intercept of left ventricular end-diastolic volume–stroke work relation was significantly less variable than the other two relations ($p < 0.05$). In addition, there was significantly less variation in the volume intercept of the end-systolic pressure-volume relation than in the volume intercept of the left ventricular end-diastolic volume–peak positive dP/dt relation ($p < 0.05$). There was no definite trend in degree of variability over the time from baseline to week 3 for any of the relations. In comparing volume intercept to slope and position, there was a divergence in the response of the various relations. For the end-systolic pressure-volume and left ventricular end-diastolic volume–peak positive dP/dt relations, volume intercept had significantly greater variation than either slope or position. In contrast, the volume intercept for the left ventricular end-diastolic volume–stroke work relation was

Table 2. Average Values for Volume Intercepts, Position Volumes and Slopes by Level of Heart Failure

	Volume Intercept (ml)		
	P_{ES}-V_{ES}	SW-V_{ED}	dP/dt-V_{ED}
Baseline	13.2 ± 2.7	27.6 ± 3.3	−8.5 ± 11.1
Week 1	15.9 ± 3.2	33.2 ± 4.2	−4.3 ± 10.7
Week 2	19.1 ± 4.6	35.9 ± 7.6	2.0 ± 9.7
Week 3	19.9 ± 6.2	45.4 ± 6.1*	−10.1 ± 10.5
	Position Volume (ml)		
	P_{ES}-V_{ES}	SW-V_{ED}	dP/dt-V_{ED}
Baseline	33.6 ± 3.9	46.2 ± 3.6	29.1 ± 19.1
Week 1	40.0 ± 4.6	59.6 ± 5.8*	44.1 ± 22.5*
Week 2	50.4 ± 6.5*	69.5 ± 7.0*	52.9 ± 29.0*
Week 3	61.2 ± 6.6*	89.3 ± 7.6*	68.6 ± 25.9*
	Slope		
	P_{ES}-V_{ES} (mm Hg/ml)	SW-V_{ED} (mm Hg)	dP/dt-V_{ED} (mm Hg/s per ml)
Baseline	6.3 ± 2.2	61.9 ± 9.1	47.1 ± 13.6
Week 1	4.5 ± 1.2	45.7 ± 5.4*	33.2 ± 7.5*
Week 2	3.6 ± 1.0	39.3 ± 4.5*	25.8 ± 6.4*
Week 3	2.8 ± 0.7*	26.5 ± 2.4*	20.3 ± 6.8*

*$p < 0.05$ vs. baseline by analysis of variance. Values presented are mean value ± SE. dP/dt-V_{ED} = left ventricular end-diastolic volume–peak positive first derivative of left ventricular pressure relation; P_{ES}-V_{ES} = end systolic pressure-volume relation; SW-V_{ED} = left ventricular end-diastolic volume–stroke work relation.

similar in variability to position and significantly less variable than the slope.

The average values for volume intercepts, positions and slopes are shown in Table 2 by level of heart failure, and an example is shown in Figure 1. The volume intercepts for the end-systolic pressure-volume and left ventricular end-diastolic volume–stroke work relations progressively but nonsignificantly increased in value as heart failure became more severe, consistent with a gradual rightward shift of each relation with progressively more severe left ventricular dysfunction. Similar, and significant, shifts in the position of V_{75} (end-systolic pressure-volume), $V_{1,000}$ (left ventricular end-diastolic volume–stroke work) and $V_{1,000}$ (left ventricular end-diastolic volume–peak positive dP/dt) were present. There was a moderate correlation between the volume intercept and V_{75} for the end-systolic pressure-volume relation ($r = 0.65$, $p < 0.00001$). There was a stronger correlation between the volume intercept and $V_{1,000}$ for the left ventricular end-diastolic volume–stroke work relation ($r = 0.82$, $p < 0.00001$). In contrast, the volume intercept for left ventricular end-diastolic volume–peak positive dP/dt was inconsistent and negative in many cases, showing no significant progression with worsening heart failure.

Analysis of the response of the slopes of each relation are shown in Table 2. All three relations responded in a similar manner and demonstrated a significant and progressive decline during the development of heart failure. The data for slope and position are presented in a different format in Table 3 and are shown as percent change from baseline. Note that the relative change in position is somewhat greater than the relative change in slope, but no comparison between slope and position was significantly different. Thus, all three relations change in a relatively similar fashion. This is further demonstrated by correlation (using all runs at all levels of heart failure) for relative change in the slopes (end-systolic pressure-volume vs. left ventricular end-diastolic volume–stroke work, $r = 0.84$*; end-systolic pressure-volume vs. left ventricular end-diastolic volume–peak positive dP/dt, $r = 0.79$*; left ventricular end-diastolic volume–stroke work vs. left ventricular end-diastolic volume–peak positive dP/dt, $r = 0.67$* [*$p < 0.001$]) and positions (V_{75} [end-systolic pressure-volume] vs. $V_{1,000}$ [left ventricular end-diastolic volume–stroke work], $r = 0.87$*; V_{75} [end-systolic pressure-volume] vs. $V_{1,000}$ [left ventricular end-diastolic volume–peak positive dP/dt], $r = 0.80$*; $V_{1,000}$ [left ventricular end-diastolic volume–stroke work] vs. $V_{1,000}$ [left ventricular end-diastolic volume–peak positive dP/dt], $r = 0.68$* [*$p < 0.001$]) of the relations. For comparison, the relative change in ejection fraction and peak positive dP/dt are also shown. The correlations between the percent change in ejection fraction versus position and slope as well as the correlations with peak positive dP/dt are shown in Table 4. For both slope and position, the correlations with ejection fraction are stronger than with peak positive dP/dt, but as heart failure becomes more severe, the correlations with ejection fraction decline.

Discussion

The end-systolic pressure-volume relation has been extensively evaluated in isolated heart preparations and in the intact circulation (1–3). In most studies, normal hearts have been subjected to short-term interventions that vary contractility or loading conditions. It has been shown that this relation is able to accurately assess contractility and that it is relatively independent of loading conditions (1–8,18–23). However, the studies have raised several concerns with regard to the underlying variability of the measurements, the dependency of results on the form of intervention used to produce variably loaded beats, the accuracy of the assumption that the end-systolic pressure-volume relation is linear, the possibility that the relation is affected by changes in left ventricular cavity size and shape and the fact that intrinsic diastolic dysfunction may affect the relation (3–7,11,19–24). These concerns raise the question: Is the end-systolic pressure-volume relation suitable for serial analysis of the progressive development of left ventricular dysfunction in the intact circulation?

Previous studies. Previous use of the end-systolic pressure-volume relation in failing hearts has been predominantly studied in humans during cardiac catheterization. Most of the studies have used a limited number of pressure-volume loops generated by pharmacologic manipulation of loading condi-

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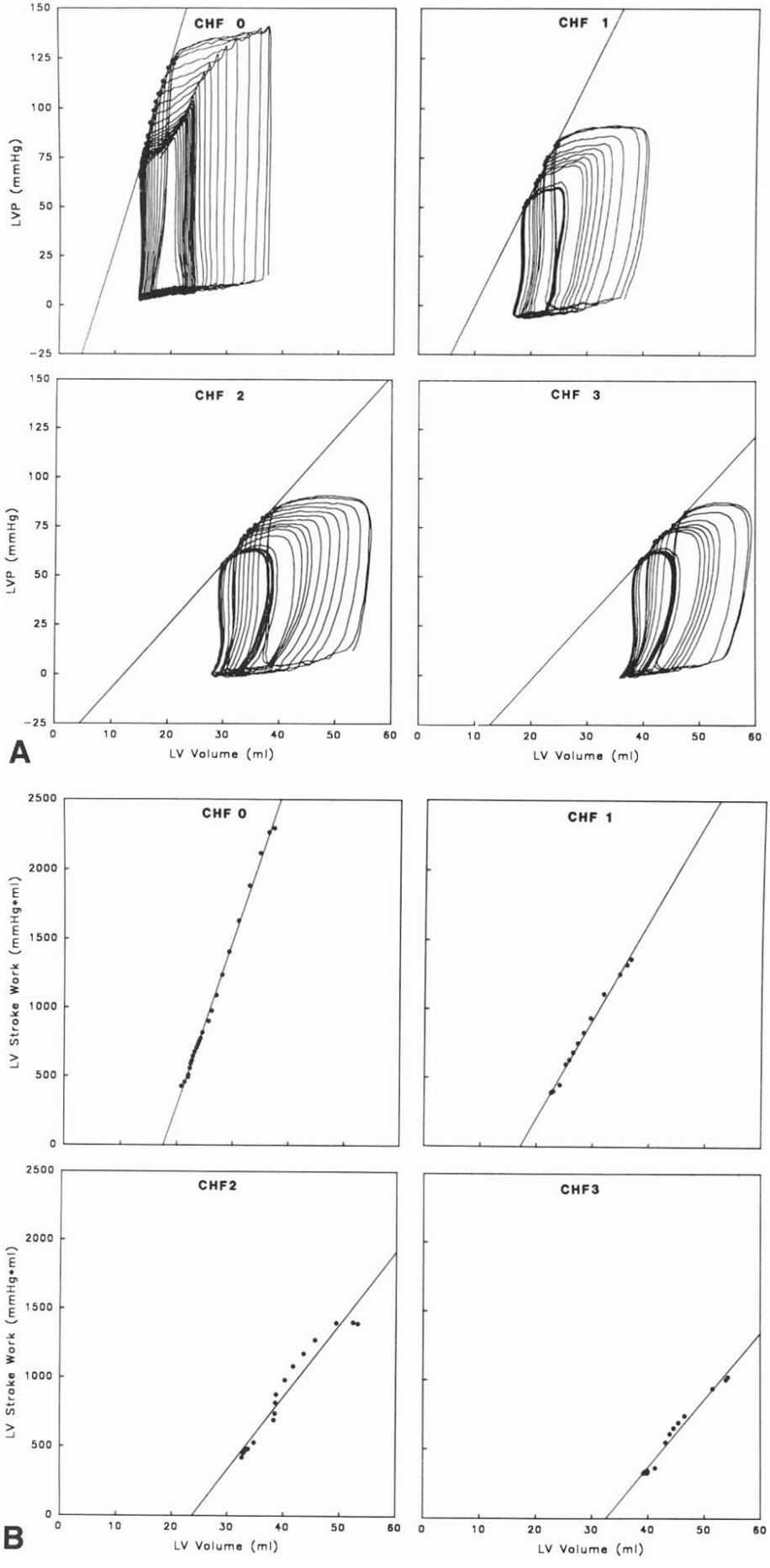

Figure 1. A, Series of left ventricular (LV) pressure (P)-volume loops obtained at baseline and three levels of congestive heart failure (CHF): CHF 1 = mild failure; CHF 2 = moderate failure; CHF 3 = severe failure. There is a progressive decline in slope, a rightward shift and a reduction in systolic pressure as failure becomes more severe. B, Plot of stroke work versus left ventricular (LV) end-diastolic volume used to derive the left ventricular end-diastolic volume–stroke work relation. The plots were derived from the same data as in A. There is a progressive decline in slope and a rightward shift in the relation. C (opposite page), Plot of peak positive first derivative of left ventricular pressure (dP/dt) versus left ventricular end-diastolic volume used to derive the left ventricular end-diastolic volume–peak positive dP/dt relation. Plots are derived from data shown in A. There is a progressive decline in slope and a rightward shift in the relation.

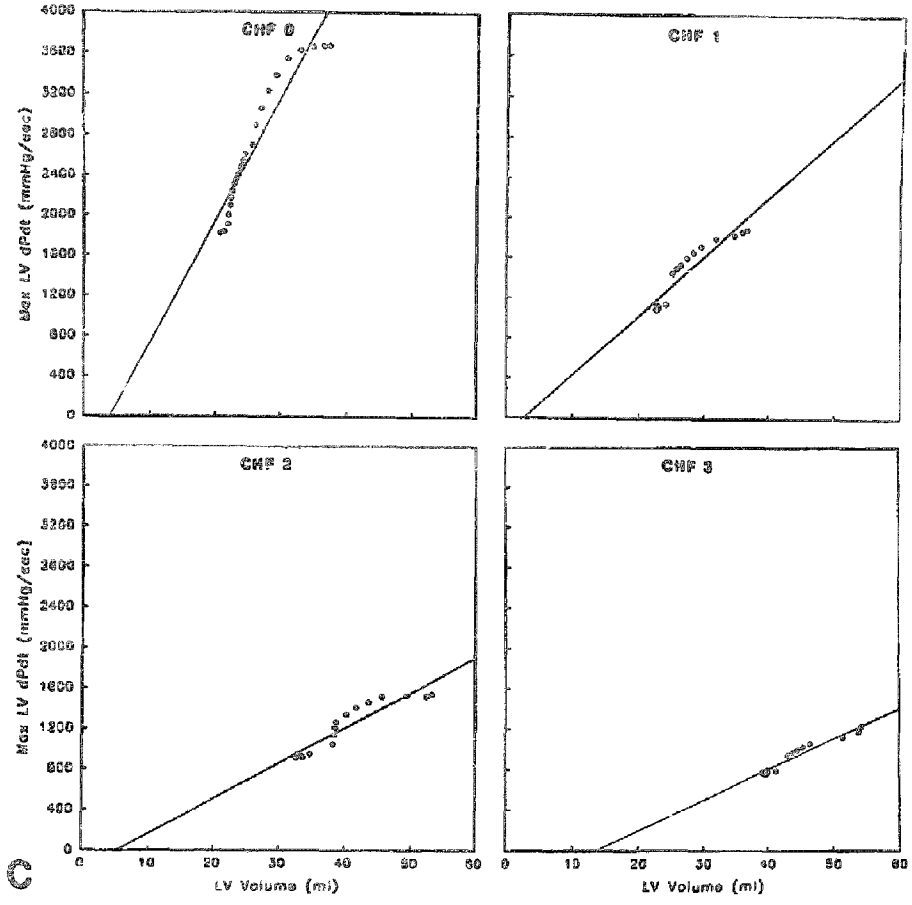

Figure 1 (continued). See legend on opposite page.

tions over a relatively narrow range of pressure and volumes. However, it has recently been shown by VanFossen et al. (23) and Kass and Maughan (3) that inferior vena cava occlusion can be safely performed in patients with heart failure to develop a series of variably loaded pressure-volume loops, and Baur et al. (13) have recently evaluated 11 patients with dilated cardiomyopathy before and after introduction of enalapril using these techniques. Grossman et al. (24), utilizing contrast ventriculography and micromanometer catheters, obtained end-systolic pressures and end-ejection volumes in 24 patients with a wide range of left ventricular performance. They showed that slope declines and volume intercept increases as left ventricular performance declines. Mehmel et al. (25) evaluated 11 patients with coronary artery disease and 1 patient with dilated cardiomyopathy, obtaining three end-ejection volumes and

Table 3. Relative Change in Slope and Position From Baseline for Each Level of Heart Failure Induced by Tachypacing

	Week 1	Week 2	Week 3
Slope (%)			
P_{ES}-V_{ES}	−11.9 ± 12.1	−21.9 ± 19.6	−43.0 ± 6.7
SW-V_{ED}	−19.5 ± 9.7	−27.6 ± 10.2	−51.9 ± 5.6
dP/dt-V_{ED}	−16.0 ± 13.6	−22.0 ± 18.3	−47.3 ± 8.2
Position volume (%)			
P_{ES}-V_{ES}	23.4 ± 7.1	53.7 ± 12.6	78.0 ± 17.3
SW-V_{ED}	32.6 ± 12.2	50.9 ± 10.6	87.4 ± 17.8
dP/dt-V_{ED}	36.8 ± 9.1	74.4 ± 20.2	119 ± 26.9
LVEF (%)	−26.6 ± 6.8	−39.5 ± 8.3	−54.2 ± 8.1
+dP/dt (%)	−17.3 ± 4.0	−27.5 ± 5.3	−38.1 ± 2.7

Values presented are mean value ± SE (% change from baseline). LVEF = left ventricular ejection fraction; other abbreviations as in Tables 1 and 2.

Table 4. Correlation of Relative Change in Slope and Position Versus Ejection Fraction and Peak Positive First Derivative of Left Ventricular Pressure

	Week 1	Week 2	Week 3
Left Ventricular Ejection Fraction			
Slope			
P_{ES}-V_{ES}	0.73*	0.51	0.26
SW-V_{ED}	0.85*	0.65*	0.48
dP/dt-V_{ED}	0.78*	0.39	0.64*
Position volume			
P_{ES}-V_{ES}	−0.78*	−0.68*	−0.45*
SW-V_{ED}	−0.64*	−0.67*	−0.59
dP/dt-V_{ED}	−0.72*	−0.24	−0.29
Peak +dP/dt			
Slope			
P_{ES}-V_{ES}	0.63*	0.10	0.38
SW-V_{ED}	0.51	0	0.56
dP/dt-V_{ED}	0.71*	0.61*	0.23
Position volume			
P_{ES}-V_{ES}	−0.16	0.18	−0.13
SW-V_{ED}	0	0.21	−0.25
dP/dt-V_{ED}	−0.34	−0.29	−0.28

*$p < 0.05$. Abbreviations as in Tables 1 and 2.

end-systolic pressures. The end-systolic pressure-volume relation appeared to be linear, and the slope was found to be exponentially related to ejection fraction. However, volume intercept was unrelated to any other measures of contractility.

Using end-ejection derived from the radionuclide ventriculogram and end-systolic pressure, Konstam et al. (26) constructed 3 to 4 variably loaded beats in 10 patients with heart failure. A linear relation was obtained in both the left and the right ventricle. The slope and intercept values of the right ventricle correlated with other measures of ventricular function, but the corresponding relations for the left ventricle were only moderate.

Full pressure-volume loops have also been generated in patients with dilated cardiomyopathy. Aroney et al. (27), also using radionuclide ventriculography, produced three to four pressure-volume loops in nine patients. Using the end-systolic pressure-volume relation, these investigators showed that a linear relation was present and that the slope was exponentially related to ejection fraction. However, attempts to use the isochronal maximal elastance relation were unsuccessful, and their evaluation of the left ventricular end-diastolic volume–stroke work relation was found to be nonlinear. The slope values for the end-systolic pressure-volume relation for the left ventricle were found to be similar to those obtained by Konstam et al. (26). Hermann et al. (28) also generated full pressure-volume loops in dilated cardiomyopathy. The phosphodiesterase inhibitor enoximone was then given, the relation moved upward and leftward, consistent with an increase in contractility.

Serial evaluation of heart failure. Experience with end-systolic indexes of performance in the serial evaluation of the failing heart are quite limited (13). Morgan et al. (29) tachypaced (using atrial tachypacing) eight dogs for 2 weeks and compared the ratio of systolic blood pressure to end-systolic volume index and also the ratio of end-systolic wall stress to end-systolic volume index. Both ratios declined significantly compared with baseline. Wolff et al. (30), using a blood-perfused isolated heart preparation, have recently compared the end-systolic pressure-volume relation and stroke work relations in dogs that underwent tachypacing for 26 days with control dogs. They found a consistent decrease in slope of both relations compared with baseline and a change in position of the end-systolic pressure-volume relation (30). The present study extends previous work done in normal hearts (11) to the failing heart by evaluating a large number of variably loaded pressure-volume loops used to construct three separate methods of assessing left ventricular performance. It also extends previous work done in the failing heart (29–31) by assessing serial changes in left ventricular performance during the development of heart failure using variably loaded pressure-volume loops not dependent on pharmacologic manipulation.

End-systolic relations. Three distinctly different methods of quantitating left ventricular performance were chosen for comparison. All three are easily derived from variably loaded pressure-volume loops. The end-systolic pressure-volume relation utilizes a single point at end-systole defined as the maximum of Pressure/(Left ventricular volume − volume intercept) (17). Previous studies have suggested that the end-systolic pressure-volume relation works effectively in the intact circulation where resistive loads and ejection time may vary considerably (3). This may be particularly important because ventricular loading conditions and cardiac output did vary as more severe failure developed in this study.

The left ventricular end-diastolic volume–stroke work relation incorporates information from the entire cardiac cycle and thus is dependent on events that occur both at end-systole and end-diastole. This relation appears to be independent of preload and is probably relatively independent of afterload within a physiologic range of values (10,32). One advantage of the left ventricular end-diastolic volume–stroke work relation is that it generates a larger range of values for a given caval occlusion run than either the end-systolic pressure-volume relation or the left ventricular end-diastolic volume–peak positive dP/dt relation (11). It has also been found to be linear within the physiologic range (7,10,11). It is unclear whether the left ventricular end-diastolic volume–stroke work relation is independent of changes in geometry of the left ventricular chamber or is affected by changes in filling of the left ventricle.

The left ventricular end-diastolic volume–peak positive dP/dt relation is derived from the isovolumetric contraction period of the cardiac cycle. This measurement is directly related to the original time-varying elastance model and is thus directly related to maximal elastance. Previous studies have demonstrated that this relation is substantially linear throughout the physiologic range, although two studies have noted the development of curvilinearity at various preload levels (21,32). This would be of concern in the present study because of the progressive increase in preload that occurs with progressive development of heart failure (9,11,21).

One principal finding of the present study is that all three relations can be utilized in the intact circulation as progressive left ventricular dysfunction occurs. There is no evidence that variability increases as severity of left ventricular dysfunction increases. Thus, serial increases in filling pressures, reduction in ventricular performance, a reduced range of end-systolic pressures achieved during each run and a delay in the onset of pressure decline have no effect on variability. There also was no significant difference in variability among any of the three relations. This was true across all levels of left ventricular dysfunction. Similar to the results of Little et al. (11), the variability of the position of the relations was consistently less than the variability for slope.

Volume intercepts. Data from calculated volume intercepts were considerably more variable and differed markedly between relations. The volume intercept of the left ventricular end-diastolic volume–stroke work relation has a very low variability similar to that of position and appears to be a highly reproducible value that may be clinically useful.

The volume intercepts of the end-systolic pressure-volume and left ventricular end-diastolic volume–peak positive dP/dt relations are considerably more variable and thus of less value. The significantly lower variability in left ventricular end-diastolic volume–stroke work, the greater range of values achieved on a particular run and the fact that this relation appears to be linear may all contribute to the low variability of its volume intercept. Similarly, the smaller range of the left ventricular end-diastolic volume–peak positive dP/dt and end-systolic pressure-volume relations, the fact that these measurements are only one point in the cardiac cycle rather than the entire loop and the fact that the left ventricular end-diastolic volume–peak positive dP/dt relation is a differentiated value may all combine to increase the variability of volume intercept for the end-systolic pressure-volume and left ventricular end-diastolic volume–peak positive dP/dt relations. Inspection of the plots of all caval occlusion runs for all three relations showed that linear correlation was appropriate for the physiologic range of volumes examined. However, it is also possible that the left ventricular end-diastolic volume–peak positive dP/dt and end-systolic pressure-volume relations are not linear at their lower extremes and that the lower range of pressure drop obtained with progressive failure makes a linear extrapolation to volume intercept inappropriate. This may explain why position relation calculations are superior to volume intercept.

In previous studies using normal hearts, volume intercept has tended to remain unchanged as the inotropic state was changed or actually increased when a positive inotropic agent was given (6,7,11). In the isolated blood-perfused preparation of heart failure induced by tachypacing recently reported by Wolff et al. (30), where volume intercept could be directly measured, there was no change in volume intercept in the failure group compared with the control group. However, when these investigators estimated volume intercept from physiologic volumes and pressures, volume intercept tended to move rightward, similar to the present study. This could be due to an increased left ventricular volume at physiologic pressures or to loss of inotropy because any rightward shift is certainly consistent with a reduction in mechanical performance of the left ventricle. Previous studies have shown that volume intercept may shift with changes in impedance (11,32). Crude estimates showed a change in peripheral resistance but not at the most severe level of heart failure. This would suggest that peripheral resistance is not a significant factor affecting volume intercept.

Relative change in slope and position. The mean values for calculated slope and position are consistent with a progressive decline in mechanical performance of the left ventricle (Table 3, Fig. 1). The relative changes in all three indexes were similar directionally and in magnitude. For comparison, an analysis was done for ejection fraction and peak positive dP/dt. Although group mean values appear to be similar, correlations of percent change showed that there is a moderate relation with ejection fraction but a very poor relation with peak positive dP/dt, consistent with considerable individual variation. Furthermore, the overall correlation decreased as heart failure became more severe. This may reflect an increasing effect of loading conditions on ejection fraction and peak positive dP/dt.

Study limitations. The tachypacing model, although programmed to be progressive, does show some variability in development of heart failure, particularly its rate of progression. This could have made some weekly changes in left ventricular performance too small to reliably detect. It would also increase the variance of group mean measurement across the study. As heart failure became more severe, the absolute range of pressures available to generate the variably loaded loops decreased. Although potentially a significant problem, the lack of increase in coefficients of variation suggests that this is not a significant limitation of this technique. Changes in diastolic function, which also evolve as heart failure develops, could have affected calculation of the relations, particularly the left ventricular end-diastolic volume–stroke work relation because it incorporated the entire cardiac cycle (22,33). Geometric changes should not have affected the calculations because no consistent shape changes were observed throughout the protocol. It is possible, however, that shape changes might affect the efficacy of these end-systolic variables in a more completely remodeled left ventricle caused by more severe long-standing failure than this study could induce. Thus, extrapolation of these findings to a markedly remodeled end-stage left ventricle are not possible. Recently, Howard et al. (34) showed that a more intense level of rapid pacing can produce remodeling with associated shape changes in the dog (34).

Conclusions. All three relations consistently describe changes in left ventricular mechanical performance that occur during induced heart failure despite a large array of changes in loading and performance of caval occlusion. Evolution of left ventricular dysfunction appears to cause both a rightward shift and a decline in slope. Thus, the position of the relation appears to be the most sensitive and least variable indicator of systolic performance for serial assessment of left ventricular performance in evolving heart failure.

I am grateful for the considerable technical assistance in instrumentation, data acquisition and animal care provided by Alice M. Eggleston, MS, Catherine R. Kidd, BS and Larry F. Whitesell, BS. I am also grateful to Becky Zart for expert assistance in preparation, and William P. Miller, MD for critical review, of the manuscript.

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